Application of 2-cyano-10-(2-methyl-3-(methylamino)-propyl)phenothiazine or a pharmaceutically acceptable salt as medicament

This application claims the benefit of U. S. Provisional Application No. 60/459,812, filed April 2, 2003 and benefit of priority of French Patent Application No. 03/01,440, filed February 7, 2003.

BACKGROUND OF THE INVENTION

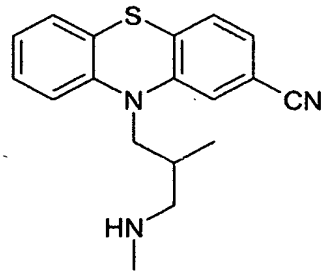
Field of the Invention

This invention relates to application of 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine to produce a medicament intended for the treatment of sleep disorders.

Description of the Art

More specifically, the present invention relates to the use of 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) or a pharmaceutically acceptable salt thereof to produce a medicament intended for the treatment of sleep disorders, anxiety disorders (generalized anxiety, panic disorder, with or without agoraphobia, post-traumatic stress condition, anxiety disorder due to a general condition, adaptation disorder with an anxious mood, acute stress condition, nonspecific anxiety disorder, minor anxiety, substance-induced anxiety

disorder, and the like), mood disorders (major depressive episode, manic episode, mixed episode, bipolar disorders, nonspecific mood disorder, nonspecific depressive disorder), mixed anxiety-depression disorder, acute and chronic psychotic states (schizophrenia, schizophreniform disorder, schizo-affective disorder, delusional disorder, brief psychotic disorder, substance-induced psychotic disorder, nonspecific psychotic disorder, psychotic disorder due to a general medical condition), behavioral disorders (agitation, aggressiveness, and the like), addiction to and withdrawal from a substance (nicotine, alcohol, benzodiazepine, cocaine, cannabis, hallucinogens, amphetamines), extrapyramidal events induced by antipsychotics (preventive and/or curative treatment), or symptomatic dimensions during acute or chronic psychotic states as monotherapy or in combination with other antipsychotics.



(I)

It is known from the prior art of 1959, GB 805 886, that products derived from 10-phenothiazine can be used as vegetative nervous system inhibitor.

The process for producing 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) is disclosed in GB 805 886.

SUMMARY OF THE INVENTION

More particularly, the present invention relates to the use of 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) or a pharmaceutically acceptable salt thereof to produce a medicament intended for the treatment of sleep disorders.

DETAILED DESCRIPTION OF THE INVENTION

Sleep disorders affect approximately 30 to 35% of the population, according to an enquiry by G.D. Mellinger (Arch. Gen. Psychiatry, 1985, 42, 225-232).

This illness is currently treated mainly with hypnotic benzodiazepines or related benzodiazepines, H1 antihistamines or sedative neuroleptics. There are molecules in development which act on receptors of histamine H3 type or serotoninergic receptors of 5-HT2a type.

It has been found that 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) exhibits an advantageous binding profile with regard to the receptors with a very good affinity ratio with regard to 5-HT2a/D2 and an excellent selectivity with regard to the muscarinic M1 receptor in comparison with the

other muscarinic M2 and M3 receptors. These results make it possible to affirm that 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine has a very good tolerance profile in particular with fewer extrapyramidal effects and fewer anticholinergic effects. This is because, according to Can. J. Psychiatry, 2002, 47(1), 27-38, the risk of appearance of extrapyramidal events during antipsychotic treatment is inversely proportional to the degree of binding to the 5-HT2a receptors and to the 5-HT2a/D2 affinity ratio. Furthermore, 2-cyano-10-(2-methyl-3-(methylamino)-propyl)phenothiazine exhibits a high affinity for 5-HT2c receptors, the role of which in anxiety disorders is currently well established.

The results of this study of binding to these various membrane receptors of central neuromediators of human origin are presented in Table 1.

Table 1

Receptors	2-Cyano-10-(2-methyl-3-(methylamino)-propyl)phenothiazine	
	IC_{50} (nM)	Ki (nM)
D2 (h)	31	12
M_1 (h)	21	17
M_2 (h)	368	251
M_3 (h)	5 490	3 920
5-HT_{1A} (h)	460	184

5-HT_{2A} (h)	9.0	1.5
5-HT_{2C} (h)	23	8.5
H_1 (h)	22	9.3

These excellent results make it possible to say that the side effects will be reduced in comparison with the currently existing products.

The sedative activity of the product was determined with mice according to an actimetry test. The actimeter is a device composed of 6 transparent cages in which the animals are individually placed. Photoelectric cells make it possible to detect movements in the cages (by cutting the beam). The spontaneous motor activity is recorded for 10 minutes. The results are expressed in the mean form and in the form of percentage of activity with respect to the control batch. The results are expressed in Table 2.

Table 2

Doses mg/kg	0.75	1	2	4
% of activity/control	61%	63%	26%	9%

Mention may in particular be made, as pharmaceutically acceptable salts, of the addition salts with inorganic acids, such as hydrochloride, sulfate, nitrate or phosphate, or organic acids, such as acetate, propionate, succinate, oxalate, benzoate, fumarate, maleate, methanesulfonate, isethionate,

theophyllineacetate, salicylate, phenolphthalinate, methylenebis(β-hydroxynaphthoate) or derivatives from substitution of these derivatives.

The medicaments are composed of 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) or a pharmaceutically acceptable salt thereof, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product, which can be inert or physiologically active. The medicaments according to the invention can be employed orally or parenterally.

The present invention relates to the use of 2-cyano-10-(2-methyl-3-(methylamino)propyl)-phenothiazine (I) or a pharmaceutically acceptable salt thereof for the preparation of pharmaceutical compositions.

Tablets, pills, powders (cachets, gelatin capsules) or granules can be used as solid compositions for oral administration. In these compositions, the active principle according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under a stream of argon. These compositions can also comprise substances other than the diluents, for example one or more lubricating agents, such as magnesium stearate or talc, a coloring agent, a coating (dragées) or a glaze.

Pharmaceutically acceptable solutions, suspensions, emulsions, and syrups and elixirs comprising inert diluents, such as water, ethanol, glycerol, vegetable oils or liquid paraffin, can be used as liquid compositions for oral administration. These compositions can comprise substances other than the diluents, for example wetting, sweetening, thickening, flavoring or stabilizing products.

The sterile compositions for parenteral administration can preferably be suspensions, emulsions or aqueous or nonaqueous solutions. Water, propylene glycol, a polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for example ethyl oleate, or other suitable organic solvents can be employed as solvent or vehicle. These compositions can also comprise adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization can be carried out in several ways, for example by aseptic filtration, by incorporating sterilizing agents in the composition, by irradiation or by heating. They can also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other injectable sterile medium.

The doses depend on the desired effect, on the duration of the treatment and on the administration

route used; they are generally between 10 and 300 mg per day orally for an adult with unit doses ranging from 10 to 300 mg of active substance.

Generally, the doctor will determine the appropriate dosage depending on the age, weight and all the other factors specific to the subject to be treated.

The following examples illustrate medicaments according to the invention:

Example A

Tablets comprising a dose of 25 mg of active product are prepared according to the usual technique. These tablets have the following composition:

Product	25 mg
Lactose	60 mg
Wheat starch	45 mg
Hydrated silica	4.5 mg
Alginic acid	2.25 mg
Talc	0.75 mg
Magnesium stearate	0.90 mg

Example B

An injectable solution comprising 1 g of active product is prepared. This solution has the following composition:

Product	1 g
Ascorbic acid	0.1 g

Monothioglycerol	0.3 g
Polyethylene glycol 400	0.02 g
Water for Injections	q.s. for 100 ml

The invention also relates to the process for the preparation of medicaments of use in the treatment of sleep disorders which consists in mixing 2-cyano-10-(2-methyl-3-(methylamino)propyl)phenothiazine (I) or its pharmaceutically acceptable salts with one or more compatible and pharmaceutically acceptable diluents and/or adjuvants.